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Predictors and outcomes of recurrent venous thromboembolism in elderly patients

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Authorship: S. Lauber, A. Limacher, T. Tritschler, O. Stalder, and D. Aujesky were responsible for study design. A. Limacher and O. Stalder did the statistical analyses. S. Lauber and D. Aujesky wrote the manuscript. A. Limacher, T. Tritschler, O. Stalder, M. Méan, M. Righini, M. Aschwanden, JH. Beer, B. Frauchiger, J. Osterwalder, N. Kucher, B. Lämmle, J. Cornuz, A. Angelillo-Scherrer, C. Matter, M. Husmann, M. Banyai, D. Staub, L. Mazzolai, O. Hugli, and N. Rodondi critically reviewed the manuscript. M. Méan, M. Righini, M. Aschwanden, JH. Beer, B. Frauchiger, J. Osterwalder, N. Kucher, B. Lämmle, J. Cornuz, A. Angelillo-Scherrer, N. Rodondi, and D. Aujesky collected data and obtained funding from the Swiss

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HIGHLIGHTS

- Elderly patients with venous thromboembolism have a 3-year recurrence incidence of 15%
- Unprovoked venous thromboembolism and proximal deep venous thrombosis are associated with recurrence
- Many traditional risk factors for recurrence (e.g., male sex) fail to predict recurrence in the elderly
- Recurrence carries a substantial case-fatality rate of over 20% in the elderly

ABSTRACT

Background: Little is known about predictors and outcomes of recurrent venous thromboembolism in elderly patients.

Methods: We prospectively followed up 991 patients aged ≥65 years with acute venous thromboembolism in a multicenter Swiss cohort study. The primary outcome was symptomatic recurrent venous thromboembolism. We explored the association between baseline characteristics and treatments and recurrent venous thromboembolism using competing risk regression, adjusting for periods of anticoagulation as a time-varying co-variate. We also assessed the clinical consequences (case-fatality, localization) of recurrent venous thromboembolism.

Results: During a median follow-up period of 30 months, 122 patients developed recurrent venous thromboembolism, corresponding to a 3-year cumulative incidence of 14.8%. The case-fatality of recurrence was high (20.5%), particularly in patients with unprovoked (23%) and cancer-related venous thromboembolism (29%). After adjustment, only unprovoked venous thromboembolism (sub-hazard ratio [SHR] 1.67 compared to provoked venous thromboembolism; 95% confidence interval [CI] 1.00-2.77) and proximal deep vein thrombosis (SHR 2.41 compared to isolated distal deep vein thrombosis; 95% CI 1.07-5.38) were significantly associated with recurrence. Patients with initial pulmonary embolism were more likely to have another pulmonary embolism as a recurrent event than patients with deep vein thrombosis.

Conclusions: Elderly patients with acute venous thromboembolism have a substantial long-term risk of recurrent venous thromboembolism and recurrence carries a high case-fatality rate. Only two factors, unprovoked venous thromboembolism and proximal deep vein thrombosis, were independently associated with recurrent venous thromboembolism, indicating that traditional risk

factors for venous thromboembolism recurrence (e.g., cancer) may be less relevant in the elderly.

INTRODUCTION

Venous thromboembolism, pulmonary embolism and/or deep venous thrombosis, is common and has a high impact on morbidity and mortality.[1] As venous thromboembolism tends to recur,[2,3] the risk of recurrence is an important determinant of the duration of anticoagulant therapy. Several patient characteristics are associated with recurrent venous thromboembolism, including age,[3,4] male sex,[3,5] obesity,[4] localization of venous thromboembolism,[6,7] unprovoked venous thromboembolism,[3,8] cancer-related venous thromboembolism,[2,3] prior venous thromboembolism,[9] family history of venous thromboembolism,[10] inflammatory bowel disease,[11] chronic heart failure,[12] leg paresis,[13] varicose veins,[4] elevated D-dimer at baseline,[14] or thrombophilia.[10,15] Treatment-related factors associated with venous thromboembolism recurrence include a suboptimal anticoagulation quality and the insertion of a vena cava filter,[2,16] whereas thrombolysis,[17] initial therapy with low-molecular-weight heparin (LMWH),[18] and concomitant use of statins or antiplatelet therapy may have a protective effect.[3,19] Bleeding episodes may also be followed by a higher risk of recurrent venous thromboembolism, possibly owing to the interruption of anticoagulation.[20] Elevated D-dimer after stopping anticoagulation and residual vein obstruction are also associated with recurrent venous thromboembolism.[21,22]

Although elderly patients have a higher risk of venous thromboembolism due to multimorbidity and an prothrombotic hemostasis[23,24] and persons aged ≥65 years comprise 55% of patients with acute venous thromboembolism,[20] little is known about predictors and outcomes of recurrent venous thromboembolism in older patients. Prior studies reporting predictors of recurrent venous thromboembolism in the elderly were limited by a retrospective study design,[20] use of administrative rather than clinical data,[20] lack of information on anticoagulation duration or quality,[12,20] or a follow-up of up to three months only.[12] To fill this gap of knowledge, we explored the

association between patient characteristics, treatments, and the long-term risk of recurrent venous thromboembolism in a prospective cohort of elderly patients with acute venous thromboembolism. We also assessed the localization and the clinical consequences of recurrent venous thromboembolism.

METHODS

Cohort sample

The study was conducted between September 2009 and December 2013 as part of a prospective multicenter cohort study that assessed long-term medical outcomes and quality of life in elderly patients with symptomatic venous thromboembolism from all five university and four high-volume non-university hospitals in Switzerland. Consecutive patients aged ≥65 years with objectively confirmed symptomatic pulmonary embolism and/or deep vein thrombosis were identified in the inpatient and outpatient services of all participating study sites. Exclusion criteria were inability to provide informed consent (i.e., severe dementia), conditions incompatible with follow-up (i.e., terminal illness or place of living too far away from the study center), insufficient German or French-speaking ability, thrombosis at a different site than lower limb, catheter-related thrombosis or previous enrollment in the cohort. The study was approved by the institutional review board at each participating site. A detailed description of the study methods was published elsewhere.[25]

Data collection

Trained study nurses recorded baseline demographics (age, sex, body mass index), localization of index venous thromboembolism (pulmonary embolism, proximal deep vein thrombosis, distal deep vein thrombosis), type of index venous thromboembolism (provoked, unprovoked, cancer-related venous thromboembolism), medical history (current hospitalization, prior venous thromboembolism, family history of venous thromboembolism, inflammatory bowel disease, chronic heart failure, hemiparesis, hemiplegia or paraplegia, prior varicose vein surgery), laboratory findings (D-dimer values, Factor V Leiden mutation, prothrombin G20210A mutation),

medications at baseline (statins, antiplatelet therapy), and venous thromboembolism-related treatments, including type of initial parenteral anticoagulation (LMWH, unfractionated heparin, fondaparinux, and danaparoid), thrombolysis, the insertion of a vena cava filter, and use of vitamin K antagonists, from all enrolled patients using standardized data collection forms.

Predictors of recurrent VTE

We abstracted the following patient baseline variables that have previously been described as predictors of venous thromboembolism recurrence from our database: age,[3,4] male sex,[3,5] obesity (defined as BMI ≥30kg/m^2),[4] localization of index venous thromboembolism (pulmonary embolism, proximal deep vein thrombosis, distal deep vein thrombosis),[6,7] type of index venous thromboembolism (provoked, unprovoked, cancer-related),[3,8] prior venous thromboembolism,[9] family history of venous thromboembolism,[10] inflammatory bowel disease,[11] chronic heart failure,[12] leg paresis (hemiparesis, hemiplegia, paraplegia),[13] varicose vein surgery (a proxy for varicose veins),[4] D-dimer levels at baseline,[14] and thrombophilia (factor V Leiden or prothrombin G20210A mutation).[10,15] Provoked venous thromboembolism was defined as venous thromboembolism following major surgery, estrogen therapy or immobilization (bed rest for more than 72 hours, travel in a sitting position for more than six hours, fracture or a cast of the lower extremity) during the last three months. We also abstracted the following treatment-related variables: use of statins and antiplatelet drugs at baseline,[19,3] type of initial anticoagulation,[18] systemic and catheter-related thrombolysis,[17] the insertion of a vena cava filter,[2] and all INR values measured during follow-up.[16]

Study outcomes

The study outcome was the time to a recurrent venous thromboembolism following the index event, defined as new or recurrent pulmonary embolism or deep vein thrombosis (proximal and/or distal) based on previously published criteria.[26,27] We also assessed the occurrence of major bleeding, defined as fatal bleeding, a symptomatic bleeding in a critical site or organ (intracranial, intraspinal, intraocular, retroperitoneal, intraarticular, pericardial or intramuscular with compartment syndrome), a bleeding with a reduction in hemoglobin concentration of ≥ 20g/l or a bleeding leading to a transfusion of ≥2 units of packed red blood cells.[28]

Follow-up included one telephone interview and two surveillance face-to-face evaluations during the first year of study participation and then semiannual contacts, alternating between telephone calls and face-to-face evaluations (clinic visits or home visits in house-bound patients), as well as periodic reviews of patient's hospital chart in order to obtain information about the data and type of clinical events. If a clinical event had occurred, this information was complemented by reviewing medical charts and interviewing patient's primary care physicians and family members. Moreover, nurses obtained information about the cause of death from hospital discharge letters and autopsy reports if available. A committee of three independent blinded clinical experts adjudicated all outcomes and classified the cause of death as definitely due to pulmonary embolism, possibly due to pulmonary embolism, or due to another cause. Death was judged to be a definite fatal pulmonary embolism if it was confirmed by autopsy or if it followed a clinically severe pulmonary embolism. Death in a patient who died suddenly without obvious cause was classified as possible fatal pulmonary embolism. Final classification was made on the basis of the full consensus of this committee. We also determined the localization of recurrent venous thromboembolism.

Statistical analyses

We compared baseline characteristics among patients with and without recurrence of venous thromboembolism using the chi-squared test and the non-parametric Wilcoxon rank-sum test as appropriate. We estimated the cumulative incidence of recurrent venous thromboembolism by localization (pulmonary embolism, proximal deep vein thrombosis, distal deep vein thrombosis) and type (provoked, unprovoked, and cancer-related) of the index venous thromboembolism event using Kaplan-Meier curves and compared groups using the log-rank test. In patients taking vitamin K antagonists, we compared the quality of anticoagulation, expressed by the time within the therapeutic INR range, in patients with and without recurrent venous thromboembolism. We calculated the mean percentage of time spent within (2.0-3.0), above (>3.0), and below (<2.0) the therapeutic INR range according to Rosendaal's method.[29] We also assessed the number of patients with a subtherapeutic anticoagulation (INR<2.0) at the time of recurrence and the number of patients with a major bleeding within three months prior to the venous thromboembolism recurrence.

We explored the association between predictors and the time to a first venous thromboembolism recurrence using competing risk regression,[30] accounting for non-venous thromboembolism-related death as a competing event. The method yields sub-hazard ratios (SHR) with corresponding 95% confidence intervals (CIs). We included all baseline characteristics and treatments into the models, except the insertion of a vena cava filter, because the number of patients with recurrent venous thromboembolism who received a filter was too small (n=2). To avoid model overfitting and instability, the models generally included a minimum of five events per

predictor variable.[31] In addition, we included only patient baseline characteristics into the model in a sensitivity analysis, omitting all treatment variables.

In the principal model, missing values were imputed using chained equations. Imputation models were based on all other variables as well as indicator variables for venous thromboembolism recurrence and death, and the duration of follow-up. In total, 20 imputed data sets were generated, which were analyzed as described above using Rubin's rules to combine results across data sets.[32] In a secondary model, patients with missing values were excluded (complete case analysis). Both analyses were repeated for the time after stopping anticoagulant therapy. All analyses were done using Stata 14 (Stata Corporation, College Station, Texas).

RESULTS

Study sample

Of 1863 screened patients with venous thromboembolism, we excluded 462 who had ≥1 exclusion criterion and 398 who did not consent to participate (Figure 1). After the exclusion of another 12 patients who refused the use of their data or withdrew from the study within one day of enrollment, our final sample comprised 991 patients. The median age was 75 years and 53% were men. Overall, 687 patients (69%) had pulmonary embolism ± deep vein thrombosis, 224 patients (23%) proximal deep vein thrombosis ±distal deep vein thrombosis, and 80 (8%) an isolated distal deep vein thrombosis. Except the somewhat higher proportion of proximal deep vein thrombosis as the initial event among patients with recurrent venous thromboembolism (34% vs. 21%), baseline characteristics and treatments did not differ between patients with and without recurrent venous thromboembolism (Table 1). Overall, 11 patients (1.1%) died from the initial venous thromboembolism event.

Recurrent venous thromboembolism

The median follow-up was 30 months (interquartile range [IQR] 19-36). The overall cumulative incidence of recurrent venous thromboembolism was 14.8% at 3 years. The cumulative incidence of venous thromboembolism recurrence was 13.1% for patients with pulmonary embolism ± deep vein thrombosis, 20.9% for patients with proximal deep vein thrombosis ±distal deep vein thrombosis, and 12.1% for patients with isolated distal deep vein thrombosis (P=0.047 by the logrank test) (Figure 2, Panel A). The cumulative incidence of recurrent venous thromboembolism did not differ by type of venous thromboembolism and was 12.6% for patients with provoked venous thromboembolism, 15.3% for patients with unprovoked venous

thromboembolism, and 16.2% for patients with cancer-related venous thromboembolism (P=0.579 by the log-rank test) (Figure 2, Panel B).

The median duration of initial anticoagulation was 7 months (IQR 4-24) and differed by localization and type of venous thromboembolism. The median duration of initial anticoagulation was 11 months (IQR 6-24) for patients with pulmonary embolism ± deep vein thrombosis, 6 months (IQR 3–20) for patients with proximal deep vein thrombosis ±distal deep vein thrombosis, and 3 months (IQR 2–6) for patients with isolated distal deep vein thrombosis. The median duration of initial anticoagulation was 6 months (IQR 3-18) for patients with provoked venous thromboembolism, 12 months (IQR 6-30) for patients with unprovoked venous thromboembolism, and 5 months (IQR 2-10) for patients with cancer-related venous thromboembolism, the latter being determined by the limited survival time.

We could assess the quality of oral anticoagulation in 821 out of 991 (83%) patients who received vitamin K antagonists and for whom INR values were available. The mean time spent in the therapeutic (2.0-3.0), supratherapeutic (>3.0) and subtherapeutic (<2.0) INR range did not differ in patients with and without venous thromboembolism recurrence (Table 2). In 31 of 122 patients (25%), the recurrent event occurred under anticoagulant therapy. At the time of recurrence, 10 of 27 (37%) patients receiving vitamin K antagonists had a subtherapeutic INR (<2.0). Of the 122 patients with recurrent venous thromboembolism, 9 (7.4%) had a major bleed within three months prior to recurrence.

Predictors of recurrent venous thromboembolism

Considering the entire follow-up period, proximal deep vein thrombosis (adjusted SHR 2.41 compared to isolated distal deep vein thrombosis; 95% CI 1.07-5.38) and unprovoked venous thromboembolism (adjusted SHR 1.67 compared to provoked venous

thromboembolism; 95% CI 1.00-2.77) as the initial event were associated with recurrent venous thromboembolism (Table 3). While proximal deep vein thrombosis as the initial event was no longer statistically significantly associated with recurrence after the initial period of anticoagulation, unprovoked venous thromboembolism remained associated with recurrence after stopping initial anticoagulation. Although patients taking statins were somewhat less likely to develop recurrent venous thromboembolism, the association between statin use and recurrent venous thromboembolism generally failed to achieve statistical significance, except for the period after stopping initial anticoagulation in the complete case analysis (adjusted SHR 0.46;
95% CI 0.23-0.93). When we included only patient baseline characteristics (without treatments) into the model, the results did not change markedly (results not shown).

Clinical characteristics and outcomes of recurrent venous thromboembolism

Of the 122 venous thromboembolism recurrences, 82 (67.2%) were pulmonary embolism ± deep vein thrombosis, 31 (25.4%) proximal deep vein thrombosis ±distal deep vein thrombosis, and 9 (7.4%) isolated distal deep vein thrombosis. Patients with initial pulmonary embolism were more likely to have recurrent pulmonary embolism than patients with initial deep vein thrombosis (74% vs. 57%) (Table 4). Patients with initial provoked venous thromboembolism were less likely to have recurrent pulmonary embolism than patients with initial unprovoked or cancer-related venous thromboembolism (50% vs.71% for each comparison). Overall, 25 of 122 (20.5%) recurrent events were fatal. The case-fatality rate was highest in patients with initial pulmonary embolism ± deep vein thrombosis (23%) and those with cancer-related venous thromboembolism (29%) (Table 4).

DISCUSSION

Our results show that elderly patients with acute venous thromboembolism have a cumulative recurrence risk of 15% within three years, with a substantial case-fatality rate of over 20% following recurrence. Among the multiple predictors explored in various analyses, only unprovoked venous thromboembolism and proximal deep vein thrombosis as the initial event were independently associated with recurrent venous thromboembolism over the entire follow-up. After stopping initial anticoagulation, only unprovoked venous thromboembolism remained associated with recurrence. Commonly cited risk factors for venous thromboembolism recurrence, such as cancer, and treatments were not consistently associated with recurrence in our sample of elderly patients. Patients with initial pulmonary embolism were more likely to have another pulmonary embolism as a recurrent event.

The 3-year cumulative incidence of recurrent venous thromboembolism in our prospective study (15%) was similar as in a retrospective study of 1048 elderly subjects (17%),[20] but slightly higher than in prior mixed retrospective/prospective cohort of 1223 elderly patients (10%).[33] While these studies did not report the case-fatality following recurrent venous thromboembolism, the case-fatality rate of 20% observed in our study of elderly subjects is substantially higher than in younger patients, with a case-fatality of 11% during the first three months of anticoagulation and case-fatality of 4% after stopping anticoagulation.[34] The case-fatality of recurrent venous thromboembolism was highest in patients initially presenting with pulmonary embolism (23%) and those with cancer-related venous thromboembolism (29%). The slightly higher cumulative incidence of venous thromboembolism recurrence in patients with proximal deep vein thrombosis as compared to patients with pulmonary embolism is most likely due to the shorter anticoagulation duration in patients with proximal deep vein thrombosis without pulmonary embolism (6 vs. 11 months).

Although we examined multiple potential predictors of venous thromboembolism recurrence, we found only two variables, unprovoked venous thromboembolism and proximal deep vein thrombosis, to be associated with recurrent venous thromboembolism. As shown in a prior study of younger patients,[35] unprovoked venous thromboembolism carries a substantial recurrence risk of up to 27% per year and long-term anticoagulant therapy is recommended in patients with unprovoked venous thromboembolism who are at low or moderate risk of bleeding.[36] Consistent with the findings from our study, an analysis of individual participants' data from seven trials showed a lower risk of recurrent venous thromboembolism after an isolated distal deep vein thrombosis compared to proximal deep vein thrombosis.[8] Evidence from a randomized trial suggests that anticoagulation may not be superior to symptomatic treatment in patients with isolated distal deep vein thrombosis and current guidelines acknowledge that symptomatic treatment and observation rather than anticoagulant treatment is possible in selected patients with isolated distal deep vein thrombosis.[36,37] Although active cancer is a well-established risk factor for venous thromboembolism recurrence,[2,3] our study and two previous studies found no association between cancer-related venous thromboembolism and recurrence in the elderly.[12,20] While we cannot exclude the possibility that cancer may be a weaker risk factor for venous thromboembolism recurrence in the elderly than in younger patients, another potential explanation for this finding is survival bias. Patients with cancer who have a very limited survival time may die from cancer before developing recurrent venous thromboembolism, mitigating the relationship between cancer and recurrence. Consistent with the results from two prior studies of older patients,[20,33] we did not find an association between advancing age and increased recurrent venous thromboembolism in elderly patients.

The localization of recurrent venous thromboembolism appears to reflect the site of the initial event in elderly patients: those with an initial pulmonary embolism more often present with recurrent pulmonary embolism again, whereas those with initial deep vein thrombosis more often have recurrent deep vein thrombosis without pulmonary embolism, a phenomenon well known in younger patients.[7] However, there is currently no evidence that the extension of anticoagulation duration in patients with pulmonary embolism is prognostically favorable.

Overall, our findings suggest that except for the type and localization of venous thromboembolism (i.e., unprovoked venous thromboembolism and proximal deep vein thrombosis), previously described clinical predictors of recurrent venous thromboembolism may not apply to the elderly and may not be particularly useful in risk-stratifying older persons with acute venous thromboembolism. As older patients with venous thromboembolism have a 2-fold risk of anticoagulation-related major bleeding, [20] it is challenging to select elderly patients with venous thromboembolism who could benefit from longer anticoagulation durations.

Our study has several potential limitations. First, our cohort included patients ≥65 years only, precluding a direct comparison of recurrence predictors and outcomes in older vs. younger patients. Second, because of the observational study design, the durations of anticoagulation differed by localization and type of venous thromboembolism, which may cause spurious associations (confounding by treatment). We attempted to minimize the risk of confounding by treatment by adjusting periods of anticoagulation as a time-varying co-variate and excluded the period of initial anticoagulation in a sensitivity analysis. Third, although the number and severity of risk factors can change over time and influence the rate of recurrent venous thromboembolism,[3] we could not assess the effect of such changes on the risk of venous thromboembolism in our cohort. Fourth, as almost no direct oral

anticoagulants were used in Switzerland during the study period, our results may not be extrapolable to patients treated with such anticoagulants. Finally, we explored a large number of potential baseline predictors and treatments but could not reliably examine the association between follow-up predictors and recurrent venous thromboembolism, such as the post-anticoagulation D-dimer level or residual vein thrombosis.

In conclusion, elderly patients with acute venous thromboembolism have a substantial long-term risk of recurrent venous thromboembolism, and recurrence has a high case-fatality rate of over 20%. Patients with initial pulmonary embolism were more likely to have another pulmonary embolism as a recurrent event. Only two factors, unprovoked venous thromboembolism and proximal deep vein thrombosis, were independently associated with recurrent venous thromboembolism, indicating that traditional risk factors for recurrent venous thromboembolism (e.g., male sex, cancer) may be less relevant in the elderly.

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FIGURE LEGENDS

Figure 1.

Patient flow chart.

Figure 2.

Panel A. Kaplan-Meier estimates of recurrent VTE by localization of the index event

The 3-year cumulative incidence for recurrent VTE was 13.1% in patients with PE±DVT, 20.9% in patients with proximal DVT±distal DVT, and 12.1% in patients with isolated distal DVT (P=0.047 by the log-rank test).

Panel B. Kaplan-Meier estimates of recurrent VTE by type of the index event

The 3-year cumulative incidence for recurrent VTE was 12.6% for provoked, 15.3% for unprovoked, and 16.2% for cancer-related VTE (P=0.579 by the log-rank test).

Figure 1

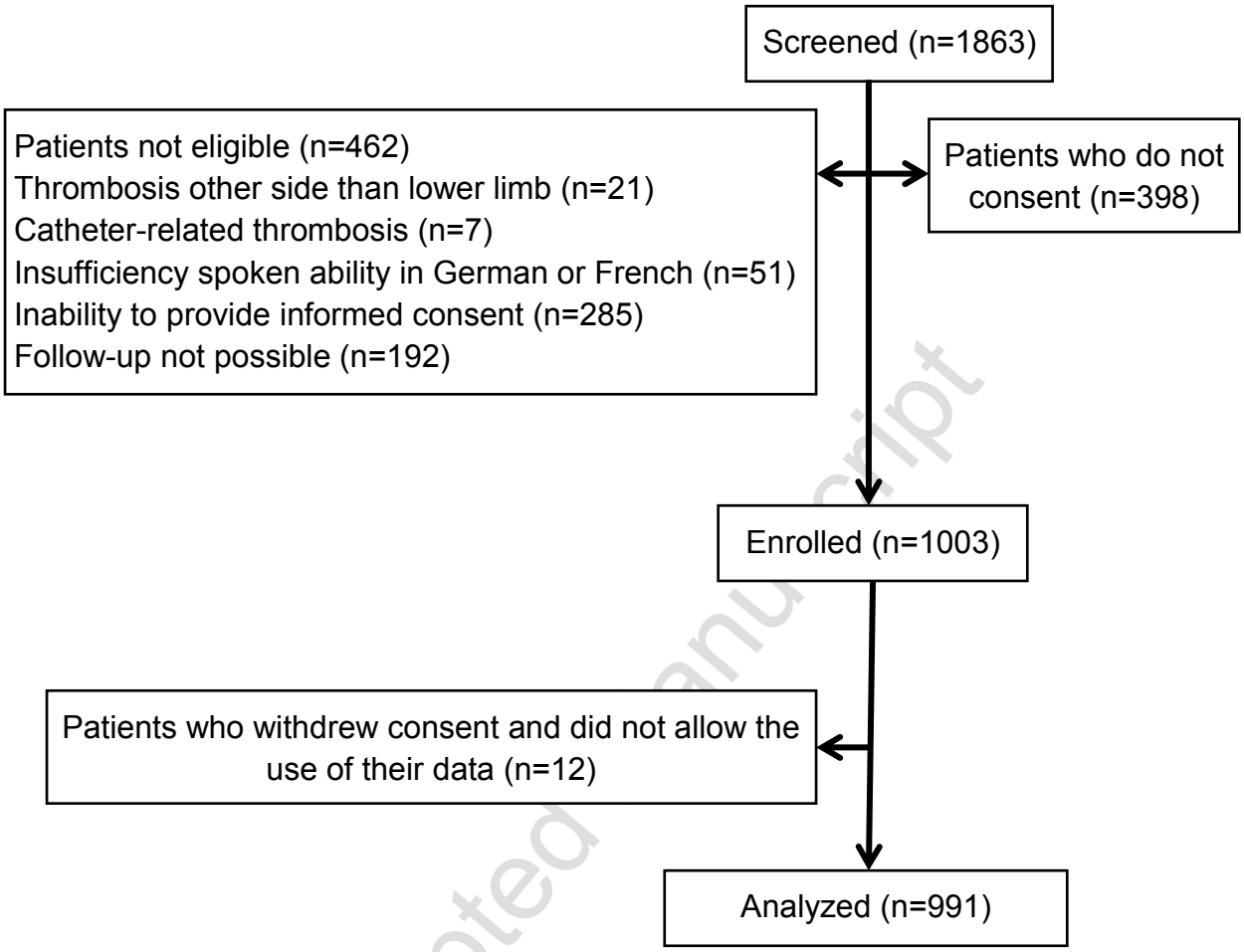
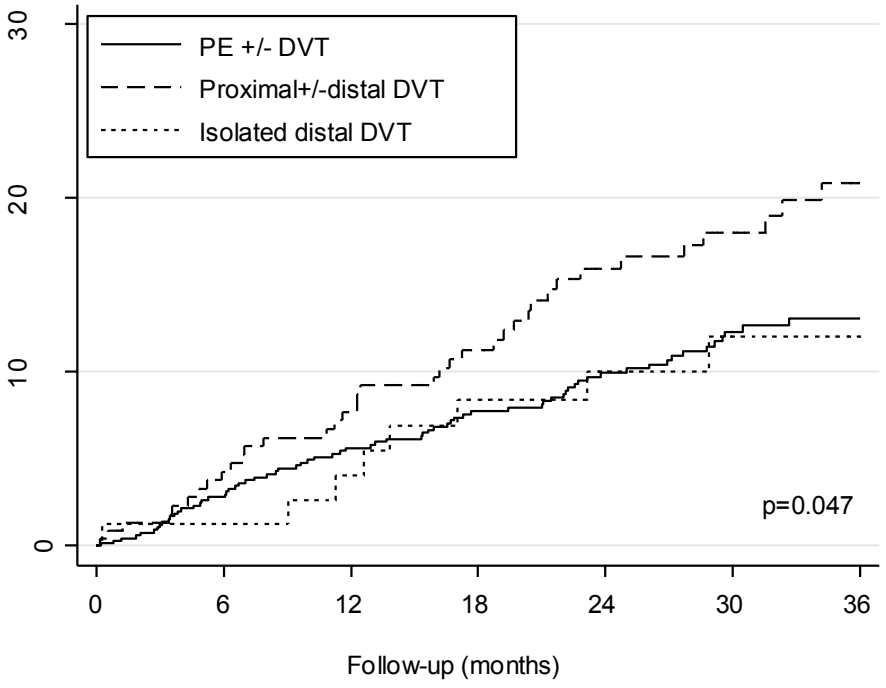


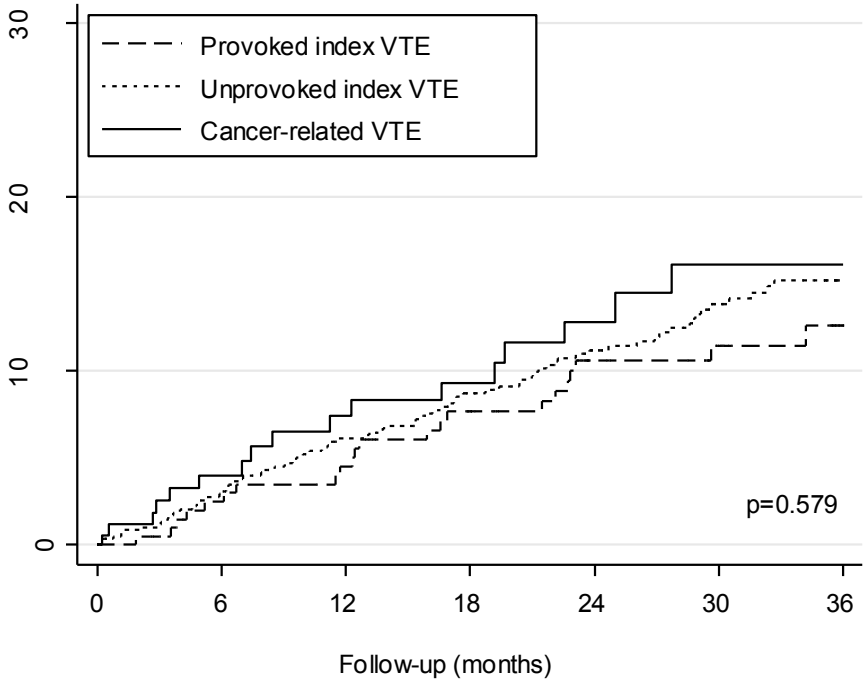
Figure 2

Panel A



Number at risk							
PE +/- DVT	687	595	554	491	384	254	156
Proximal+/-distal DVT	224	196	184	160	126	95	60
Isolated distal DVT	80	73	67	60	45	34	18

Panel B



Number at risk							
Provoked index VTE	215	192	186	164	123	87	49
Unprovoked index VTE	598	553	519	465	374	262	168
Cancer-related VTE	178	119	100	82	58	34	17

Table 1. Patient baseline characteristics and treatments by VTE recurrence

Characteristic*	All (n=991)	Recurrence (n=122)	No recurrence (n=869)	P-value
	n (%) or median (interquartile range)			
Baseline characteristics				
Patient age, years	75 (69-81)	75 (69-80)	75 (69-81)	0.838
Male sex	528 (53)	65 (53)	463 (53)	1.000
Body mass index ≥30kg/m^2	242 (24)	35 (29)	207 (24)	0.262
Localization of index VTE				0.008
PE ±DVT	687 (69)	73 (60)	614 (71)	
Proximal DVT ±distal DVT	224 (23)	41 (34)	183 (21)	
Isolated distal DVT	80 (8)	8 (7)	72 (8)	
Type of index VTE				0.176
Provoked VTE†	215 (22)	22 (18)	193 (22)	
Unprovoked VTE	598 (60)	83 (68)	515 (59)	
Cancer-related VTE‡	178 (18)	17 (14)	161 (19)	
Hospital-acquired VTE	184 (19)	16 (13)	168 (19)	0.107
Prior VTE	283 (29)	33 (27)	250 (29)	0.749
Family history of VTE	165 (17)	19 (16)	146 (17)	0.796
Inflammatory bowel disease§	32 (3)	7 (6)	25 (3)	0.101
Chronic heart failure**	76 (8)	5 (4)	71 (8)	0.145
Leg paresis††	29 (3)	4 (3)	25 (3)	0.773
Prior varicose vein surgery‡‡	136 (14)	16 (13)	120 (14)	1.000
Factor V Leiden mutation	82 (8)	10 (8)	72 (8)	1.000
Prothrombin G20210A mutation	49 (5)	5 (4)	44 (5)	0.824
D-dimer at baseline, ng/mL	2506 (1573-3817)	2730 (1744-4133)	2471 (1567-3766)	0.179
Treatments				
Statin therapy§§	241 (24)	21 (17)	220 (25)	0.055
Antiplatelet therapy***	321 (32)	39 (32)	282 (32)	1.000
Type of initial anticoagulation				0.997
Low-molecular-weight heparin	465 (47)	57 (47)	408 (47)	
Unfractionated heparin	333 (34)	41 (34)	292 (34)	
Fondaparinux	158 (16)	20 (16)	138 (16)	
Danaparoid	1 (0)	0 (0)	1 (0)	
No anticoagulation	34 (3)	4 (3)	30 (3)	
Thrombolysis†††	30 (3)	4 (3)	26 (3)	0.779
Vena cava filter	11 (1)	2 (2)	9 (1)	0.635

Abbreviations: VTE=venous thromboembolism; PE=pulmonary embolism; DVT=deep venous thrombosis.

*Data were missing for BMI (1%), family history of VTE (1%), Factor V Leiden mutation (10%), Prothrombin G20210A mutation (10%), and D-dimer at baseline (15%).

†Major surgery, estrogen therapy or immobilization (bed rest for more than 72 hours, voyage in a sitting position for more than 6 hours, fracture or a cast of the lower extremity) during the last 3 months.

‡Solid or hematologic cancer requiring chemotherapy, radiotherapy, surgery, or palliative care during the last 3 months.

§Crohn's disease or ulcerative colitis.

**Known history of systolic or diastolic heart failure, left or right heart failure, forward or backward heart failure, or a known left ventricular ejection fraction of <40%.

††Hemiparesis, hemiplegia, paraplegia.

‡‡Surgical varicose vein removal, does not include non-invasive procedures (sclerotherapy, laser radiofrequency).

§§Treatment with a statin at initial admission.

***Treatment with aspirin, clopidogrel, prasugrel, or aspirin/dipyridamole at initial admission.

†††Systemic or catheter-directed thrombolysis.

Table 2. Mean percentage of time in a given INR range

INR range*	All	VTE recurrence	No VTE recurrence	
		Mean % (SD)		P-value
2.0-3.0	62 ± 23	60 ± 26	63 ± 22	0.194
>3.0	15 ± 17	15 ± 19	15 ± 17	0.810
<2.0	23 ± 21	26 ± 24	22 ± 21	0.117

Abbreviations: VTE=venous thromboembolism; SD=standard deviation; INR=international normalized ratio.

*Data were missing for 40 of 861 (4.6%) taking vitamin K antagonists.

Table 3. Predictors of recurrent VTE

	Entire follow-up period		After initial anticoagulation only	
	Multiple imputations	**Complete case analysis**	**Multiple imputations**	**Complete case analysis**
n events / N patients	122/991	101/822	93/559	77/473
Predictors	SHR (95% CI)	SHR (95% CI)	SHR (95% CI)	SHR (95% CI)
Baseline characteristics				
Patient age, years	1.00 (0.97-1.03)	1.00 (0.97-1.03)	1.00 (0.96-1.03)	1.00 (0.96-1.04)
Male sex	0.96 (0.65-1.43)	0.97 (0.63-1.48)	0.79 (0.50-1.24)	0.82 (0.50-1.34)
Body mass index ≥30kg/m^2	1.26 (0.84-1.90)	1.40 (0.90-2.18)	1.31 (0.82-2.08)	1.48 (0.88-2.48)
Localization of index VTE				
Isolated distal DVT	Reference	Reference	Reference	Reference
PE±DVT	2.00 (0.91-4.38)	2.20 (0.91-5.32)	1.51 (0.68-3.32)	1.75 (0.72-4.26)
Proximal DVT±distal DVT	2.41 (1.07-5.38)	2.60 (1.04-6.47)	1.62 (0.70-3.76)	1.71 (0.66-4.44)
Type of index VTE				
Provoked VTE*	Reference	Reference	Reference	Reference
Unprovoked VTE	1.67 (1.00-2.77)	2.04 (1.14-3.66)	1.80 (1.02-3.16)	2.16 (1.15-4.06)
Cancer-related VTE†	1.08 (0.55-2.12)	1.29 (0.60-2.77)	1.26 (0.58-2.71)	1.55 (0.66-3.63)
Prior VTE	1.55 (1.00-2.41)	1.50 (0.92-2.43)	1.42 (0.84-2.42)	1.35 (0.76-2.40)
Family history of VTE	0.86 (0.52-1.43)	0.93 (0.54-1.59)	0.86 (0.48-1.52)	0.91 (0.49-1.68)
Inflammatory bowel disease‡	1.76 (0.80-3.88)	2.10 (0.98-4.52)	1.23 (0.43-3.52)	1.62 (0.60-4.35)
Chronic heart failure§	0.65 (0.25-1.70)	0.59 (0.21-1.67)	0.63 (0.18-2.21)	0.43 (0.10-1.89)
Leg paresis**	1.57 (0.50-4.97)	0.82 (0.18-3.75)	1.98 (0.47-8.32)	0.60 (0.07-4.86)
Prior varicose vein surgery††	1.00 (0.57-1.76)	0.95 (0.49-1.81)	0.98 (0.52-1.85)	0.85 (0.40-1.82)
Factor V Leiden mutation	0.86 (0.42-1.75)	0.77 (0.36-1.65)	0.51 (0.18-1.44)	0.43 (0.15-1.27)
Prothrombin G20210A mutation	0.97 (0.37-2.52)	1.03 (0.39-2.70)	0.72 (0.18-2.96)	0.66 (0.16-2.62)
D-dimer at baseline, ng/mL (log transformed)	1.11 (0.79-1.54)	1.09 (0.78-1.52)	1.19 (0.79-1.78)	1.15 (0.76-1.74)
Treatments				
Statin therapy‡‡	0.60 (0.35-1.04)	0.62 (0.35-1.12)	0.53 (0.28-1.02)	0.46 (0.23-0.93)
Antiplatelet therapy§§	1.31 (0.84-2.05)	1.21 (0.76-1.92)	1.16 (0.68-1.96)	1.14 (0.66-1.95)
Type of initial anticoagulation				
No anticoagulation	Reference	Reference	Reference	Reference
LMWH	1.02 (0.33-3.15)	0.71 (0.23-2.21)	0.96 (0.27-3.39)	0.71 (0.20-2.58)
Others (UFH, Fondaparinux, Danaparoid)	1.09 (0.36-3.30)	0.85 (0.28-2.56)	1.02 (0.30-3.51)	0.83 (0.24-2.90)
Thrombolysis***	1.96 (0.68-5.64)	1.84 (0.57-5.87)	0.99 (0.17-5.61)	1.38 (0.27-7.19)

Abbreviations: SHR=sub-hazard ratio; CI=confidence interval; VTE=venous thromboembolism; PE=pulmonary embolism; DVT=deep venous thrombosis; LMWH=low-molecular-weight heparin; UFH=unfractionated heparin.

*Major surgery, estrogen therapy or immobilization (bed rest for more than 72 hours, travel in a sitting position for more than 6 hours, fracture or a cast of the lower extremity) during the last 3 months.

†Solid or hematologic cancer requiring chemotherapy, radiotherapy, surgery, or palliative care during

the last 3 months.

‡Crohn's disease or ulcerative colitis.

§Known history of systolic or diastolic heart failure, left or right heart failure, forward or backward heart failure, or a known left ventricular ejection fraction of <40%.

**Hemiparesis, hemiplegia, paraplegia.

††Surgical varicose vein removal, does not include non-invasive procedures (sclerotherapy, laser radiofrequency).

‡‡Treatment with a statin at initial admission.

§§Treatment with aspirin, clopidogrel, prasugrel, or aspirin/dipyridamole at initial admission.

***Systemic or catheter-directed thrombolysis.

Table 4. Recurrence characteristics and outcomes

		Type of recurrent VTE			
	All	Fatal	PE±DVT	Proximal DVT ±distal DVT	Isolated distal DVT
Index VTE	N	n/N(%)	n/N(%)	n/N(%)	n/N(%)
All patients	122	25/122 (21)	82/122 (67)	31/122 (25)	9/122 (7)
Localization of index VTE					
PE±DVT	73	17/73 (23)	54/73 (74)	13/73 (18)	6/73 (8)
Proximal DVT±distal DVT	41	7/41 (17)	23/41 (56)	16/41 (39)	2/41 (5)
Isolated distal DVT	8	1/8 (13)	5/8 (63)	2/8 (25)	1/8 (13)
Type of index VTE					
Provoked VTE*	22	1/22 (5)	11/22 (50)	9/22 (41)	2/22 (9)
Unprovoked VTE	83	19/83 (23)	59/83 (71)	18/83 (22)	6/83 (7)
Cancer-related VTE†	17	5/17 (29)	12/17 (71)	4/17 (24)	1/17 (6)

Abbreviations: VTE=venous thromboembolism; PE=pulmonary embolism; DVT=deep venous thrombosis.

*Major surgery, estrogen therapy or immobilization (bed rest for more than 72 hours, travel in a sitting position for more than 6 hours, fracture or a cast of the lower extremity) during the last 3 months.

†Solid or hematologic cancer requiring chemotherapy, radiotherapy, surgery, or palliative care during the last 3 months.